REMARKS

The Office Action of April 7, 2004 has been reviewed and its contents carefully noted. Reconsideration of this case, as amended, is earnestly requested. Claims 1-6 and 8-9 remain in this case, claims 1 and 8 being amended and claim 7 being cancelled by this amendment. The amendment of claims 1 and 8 is supported by the original claims and throughout the specification; no new matter has been added.

The Examiner's attention is drawn to the fact that submitted herewith is Applicant's Petition and Fee for Extension of Time.

Rejections under 35 U.S.C. § 112

Claims 1-7 were rejected under 35 U.S.C. § 112, first paragraph, as lacking an enabling disclosure. Applicant respectfully disagrees with the rejection.

Claim 7 is hereby cancelled. With regard to claims 1-6, reconsideration and withdrawal of the rejection are respectfully requested.

In support of the rejection, the Examiner makes numerous assertions of fact, however, the Examiner cites no authority in support of such factual assertions. If the Examiner's assertions are intended to indicate that the rejection is based on common knowledge in the art or "well known" prior art, then Applicant hereby respectfully traverses the Examiner's assertions.

More particularly, the Examiner asserts that the gene therapy art is extremely unpredictable, particularly with regard to the use of baculoviruses as gene therapy vectors. The Examiner further asserts that the prior art provides no clinical experience using recombinant baculoviral vectors for gene therapy. Thus the Examiner concludes that the art is totally unpredictable and that the state of the art at the time of invention was "nil". Applicant respectfully disagrees.

In Dickinson v. Zurko, 119 S. Ct. 1816, 50 USPQ2d 1930 (1999), the Supreme Court held that in reviewing patentability, a reviewing court must apply the standards set forth in the Administrative Procedure Act ("APA") at 5 U.S.C. § 706 (1994), see Zurko, 119 S. Ct. at 1818, 50 USPQ2d at 1931-32.

Subsequently, in In Re Gartside, the Court of Appeals for the Federal Circuit held that section 144 explicitly provides that a court must review Board decisions "on the record" developed by the PTO (see 35 U.S.C. § 144 (1994) ("The United States Court of Appeals for the

Federal Circuit shall review the decision from which an appeal is taken on the record before the Patent and Trademark Office.") (emphasis added)), and it is for this reason that the Commissioner is required to convey the record to the court in the event of an appeal. See Id. § 143. Moreover, the "hearing" upon which the "record" is based is "provided by" 35 U.S.C. § 7(b), which states that:

> *"The Board of Patent Appeals and Interferences shall, on written appeal of an applicant, review adverse decisions of examiners upon applications for patents and shall determine priority and patentability of invention in interferences declared under section 135(a) of this title. Each appeal and interference shall be heard by at least three members of the Board of Patent Appeals and Interferences, who shall be designated by the Commissioner. Only the Board of Patent Appeals and Interferences has the authority to grant rehearings."*

35 U.S.C. § 7(b) (1994) (emphasis added). Thus, the plain language of §§ 7 and 144 of Title 35 indicates that the courts must review Board decisions "on the record of an agency hearing provided by statute," and that they must therefore review Board factfinding for "substantial evidence." See In Re Robert J. Gartside and Richard C. Norton, 99-1241 Interference No. 103,255 (Fed. Cir. 2000). See also Thomas Leonard Stoll, A Clearly Erroneous Standard of Review, 79 J. Pat. & Trademark Off. Soc'y 100, 106 (1997) (arguing in favor of "substantial evidence" review based on 35 U.S.C. §§ 7(b) and 144).

The test for enablement is whether the disclosure, when originally filed, contained sufficient information regarding the subject matter of the claims as to enable those of ordinary skill in the pertinent art to make and use the invention. The standard is whether the experimentation necessary to practice the invention is undue or unreasonable. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). See also U.S. v. Telectronics, Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.") (emphasis added).

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom.*, Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. Thus, the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

Furthermore, part of the test for enablement depends on whether those skilled in the art could make or use the invention based on Applicant's disclosures coupled with information known in the art. Applicant's specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without "undue experimentation." Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (emphasis added); In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). Indeed, a patent need not teach, and preferably omits, what is well known in the art. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies , Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

The Prior Art Teaches Successful Use of Baculoviruses for Gene Therapy Vectors

Notwithstanding the Examiner's assertions to the contrary, the prior art teaches the successful use of baculoviruses for gene therapy vectors. Attached hereto Applicant provides copies of several references that teach the use of recombinant baculoviral vectors for gene therapy, citing specific examples of clinical trials involving such vectors. Thus, it is respectfully submitted that the enablement rejection is not supported by substantial evidence or by the teachings of the prior art as a whole.

The baculovirus Autographa californica multiple nuclear polyhedrosis virus (AcMNPV) has widely been used for recombinant gene expression and is known to be transported into some primary cells and into many cell lines derived from mouse, rat, porcine, and human tissues. See, *e.g.*, Hofmann *et al.*, "Efficient gene transfer into human hepatocytes by baculovirus vectors." Proc. Natl. Acad. Sci. USA 92:10099-10103 (1995); Boyce *et al.*, "Baculovirus-mediated gene transfer into mammalian cells." Proc. Natl. Acad. Sci. U S A 93:2348-2352 (1996); Sabdug *et al.*, "Gene transfer into hepatocytes and human liver tissue by baculovirus vectors." Hum. Gene Ther. 7:1937-1945 (1996); Murges *et al.*, "Baculovirus transactivator IE1 is functional in mammalian cells." J. Gen. Virol. 78:1507-1510 (1997); Shoji *et al.*, "Efficient gene transfer into various mammalian cells, including non-hepatic cells, by baculovirus vectors." J. Gen. Virol. 78:2657-2664 (1997); Palombo *et al.*, "Site-specific integration in mammalian cells mediated by a new hybrid baculovirus-adeno-associated virus vector." J. Virol. 72:5025-5034 (1998); Fipaldini *et al.*, "Expression of hepatitis C virus cDNA in human hepatoma cell line mediated by a hybrid baculovirus-HCV vector." Virology 255:302-311 (1999); Condreay *et al.*, "Transient

and stable gene expression in mammalian cells transduced with a recombinant baculovirus vector." Proc. Natl. Acad. Sci. USA 96:127-132 (1999).

For example, baculovirus vectors are known to efficiently transfer genes into human liver cells, and have been used to deliver hepatitis B to human liver efficiently to allow study of hepatitis B drug therapy. See Delaney *et al.*, "Use of the hepatitis B virus recombinant baculovirus-Hep G2 system to study the effects of beta 2',3' dideoxy 3' thiaceydine on replication of hepatitis B virus and accumulation of covalently closed circular DNA" Antimicrob. Agents Chemother. 43, 2017-26; Hofmann *et al.*, (1999); "Efficient gene transfer into human hepatocytes by baculovirus vectors" Proc. Natl. Acad. Sci. USA 92, 10099-103 (1995); Hofmann *et al.*, "Baculovirus mediated gene therapy in the presence of human serum or blood facilitated by inhibition of the complement system" Gene Ther. 5,531-6 (1998); Boyce *et al.*, "Baculovirus-mediated gene transfer into mammalian cells" Proc. Natl. Acad. Sci. USA 93, 2348-52 (1996). Condreay *et al.* also reported stable baculovirus transduction of several mammalian cell types with expression of a reporter gene for multiple passages.

Baculovirus vectors are known to be transferred into human liver tissues most effectively in perfused liver tissue, as serum components are known to hamper virus transfer. Sandig *et al.*, "Gene transfer into hepatocytes and human liver tissue by baculovirus vectors." Human Gene Ther. 20,1937-45 (1996). Human conditions causing defects in complement are known to allow liver transfer of recombinant baculovirus, and inhibitors of complement are known to facilitate baculovirus gene transfer (Hofmann and Strauss 1998). Hybrid baculovirus-adeno virus vectors also have been used to deliver genes to human cells. See, *e.g.*, Palombo *et al.*, "Site specific integration in mammalian cells mediated by a new hybrid baculovirus-adeno-associated virus vector." J. Virol. 72, 5025-34 (1998).

More recently, scientists led by Seppo Yla-Hertualla, at the University of Kuopio (Finland), reported successful *in vivo* gene transfer in mammals using a baculovirus-mediated vector system. This was achieved using a second-generation engineered baculovirus and Eurogene, Ltd.'s (6 Warren Mews, London W1P5DJ, UK; Tel: 020 7388 7722) collar-reservoir local delivery device. The work was published in 2000 (K.J. Arrienne *et al.*, Gene Therapy 717; 1499-1503 [2000]).

Baculovirus vectors also are known to efficiently transfer genes into neural cells in culture and in rodents, French researchers report in the December 19th (2000) issue of the Proceedings of the National Academy of Sciences. Proc. Natl. Acad. Sci. USA 97:14638-14643 (2000). Indeed, according to Dr. J. Mallet from Centre National de la Recherche Scientifique, in

Paris, the nuclear polyhedrosis virus *Autographa californica* (AcNPV) is ideal for gene therapy of nondividing cells, because it is expressed episomally and its promoter is silent in mammalian cells. Dr. J. Mallet *et al.* infected two neuroblastoma cell lines, three human primary neural cultures and adult astrocytes with the virus and found efficient transduction of the virus in all but one of the neuroblastoma cell lines. Expression was improved by the addition of butyrate, which inhibits histone deacetylases, highlighting the importance of the chromatin state of the baculovirus genome in the infected cells to express the transgene. The researchers also infected telencephalic cultures from human embryonic brains and found efficient transduction, particularly of neuroepithelial, neuroblastic, and glial cells. At a multiplicity of infection of 25, the reporter gene was expressed in over 50% of transduced cells. The baculovirus also transduces neural cells after direct injection into the brains of rodents, and was not inactivated by the complement system. Within a week of injection, immunohistochemical staining showed that transduced cells were mostly astrocytes were with a few neurons.

Li Ma *et al.* demonstrate that recombinant baculoviruses can serve as efficient gene transfer vehicles for delivering foreign genes driven by mammalian promoters into human and mouse pancreatic islet cells. See "Baculovirus-Mediated Gene Transfer Into Pancreatic Islet Cells" Diabetes 49(12): 1986-1991 (2000). Using several green fluorescent protein- and LacZ-expressing constructs in a cytomegalovirus promoter cassette, Li Ma *et al.* obtained efficient gene expression in primary human and mouse islet cells. There was no impairment of glucose-stimulated intracellular free calcium responses after baculovirus infection. The authors conclude that the safety and the relative ease of construction and propagation of the virus makes the baculovirus system a useful tool for facilitating the transfer of foreign genes.

Electron microscopy demonstrated pancreatic [Beta]-cells identified by the presence of typical granules that were taking up and uncoating baculovirus (Li Ma *et al.*, Fig. 5). This result is similar to the findings of Condreay *et al.* in CHO cells and Hofmann *et al.* in HUH-7 cells incubated with a baculovirus vector.

More recently, a baculovirus was used as a gene therapy vector for gene delivery to human tumor cells. See Song *et al.*, "Combination treatment for osteosarcoma with baculoviral vector mediated gene therapy (p53) and chemotherapy (adriamycin)" Experimental and Molecular Medicine, Vol. 33(1): 46-53 (March 2001). A human osteogenic sarcoma cell line, Saos-2, was found to be highly susceptible to infection with a baculoviral vector, with nearly 100% of Saos-2 cells being able to express a lacZ reporter gene after a brief exposure to the virus at a m.o.i. of 30 pfu/cell. The production of b-galactosidase protein was 18-times greater than that in HepG2 cells, which were previously thought to be the mammalian cells most susceptible

to the baculovirus. The use a baculovirus as a cytotoxic vector for p53-defective cancer was demonstrated by destruction of Saos-2 cells (p53 -/ -) with a recombinant baculovirus containing the wild type p53 gene (BV- p53) *in vitro*. The p53 baculovirus induced apoptotic cell death in tumor cells in a dose-dependent manner with ~60% killing at an m.o.i. of 160 pfu/cell. The combined treatments of gene therapy (p53) and chemotherapy (adriamycin) resulted in synergistic and potent killing of the osteogenic sarcoma cells. For example, greater than 95% of Saos-2 cells were killed by the combination of BV-p53 (m.o.i. of 100) and adriamycin (35 ng/ml), whereas ~50% and ~55% cells were killed by BV-p53 and adriamycin alone, respectively. These results indicate that baculoviral gene delivery vectors can be used to efficiently target certain types of mammalian cells for gene therapy.

The foregoing references teach that baculoviruses were used as gene therapy vectors well before Applicant's earliest-claimed filing date (August '01). Thus, the prior art teaches the successful use of baculoviruses as gene therapy vectors, and there is no requirement for Applicant to disclose this information for the specification to enable the claimed invention. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies , Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

Applicant's disclosure additionally provides methods for making using and specific examples of improved baculovirus vectors, particularly in the form of pseudotyped baculoviruses having altered host cell recognition features. Coupled with known methods for use of baculoviruses as gene therapy vectors, Applicant's disclosure enables one of ordinary skill in the art to use pseudotyped baculoviruses as gene therapy vectors.

Furthermore, Applicant concurs with the Examiner's assertion that the level of skill in the art is high. It is further undisputed that the art of gene therapy is complex. However, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom.*, Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). Because the art is complex, the art typically engages in such experimentation and, thus, some complex experimentation is expected and therefore not undue. Id.

It is respectfully submitted that the rejection for lack of enablement is thus overcome. Applicant believes that these arguments have fully addressed the Examiner's rejections, and that

the claims are now in condition for allowance. Reconsideration and withdrawal of the rejections of claims 1-7 as lacking an enabling disclosure are therefore respectfully requested.

Claims 8 and 9 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, because it is unclear whether the genetically engineered baculovirus recited in claim 8 refers to the baculovirus of step a) or step b) of claim 1.

It is respectfully submitted that the rejection is overcome by the amendment of claim 8. Reconsideration and withdrawal of the indefiniteness rejection of claims 8 and 9 are therefore respectfully requested.

Rejection under 35 U.S.C. § 102

Claim 7 was rejected under 35 U.S.C. § 102(b) as being anticipated by Blissard *et al.* (US Pat. No. 5,750,383).

Claim 7 is hereby cancelled. Reconsideration and withdrawal of the anticipation rejection of claim 7 are respectfully requested.

Conclusion

Applicant believes the claims, as amended, are patentable over the prior art, and that this case is now in condition for allowance of all claims therein. Such action is thus respectfully requested. If the Examiner disagrees, or believes for any other reason that direct contact with Applicants' attorney would advance the prosecution of the case to finality, he is invited to telephone the undersigned at the number given below.

"Recognizing that Internet communications are not secured, I hereby authorize the PTO to communicate with me concerning any subject matter of this application by electronic mail. I understand that a copy of these communications will be made of record in the application file."

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Dated: August 13, 2004